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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,763	06/05/2006	Vincenzo De Leo	SER.105	2323

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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BORGHEST, CHRISTINA M	
ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
05/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,763	DE LEO ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,16-28 and 31-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,16-28 and 31-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/4/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed 4 February 2010 is acknowledged. Claims 1 and 31 are amended and claim 30 is newly cancelled. Claims 12, 16-28 and 31-43 are under examination.

Objections/Rejections Withdrawn

Note that all rejections over claim 30 are withdrawn since this claim was cancelled.

Claim Objections

The objection to claims 12 and 31 for informalities is withdrawn in response to Applicants' amendment of the claims to recite "follicle stimulating hormone" followed by "FSH" in parentheses.

The objection to claim 30 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in response to Applicants' cancellation of that claim.

The objection to claim 40 is objected for informalities for a typographical error is withdrawn in response to Applicants' correction of that claim.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 12, 16-28 and 30-43 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in response to Applicants' amendment of the claim to recite "reduction or treatment or reduction and treatment" in lieu of "and/or" and Applicants' cancellation of claim 30.

The rejection of claim 25 for insufficient antecedent basis for the recitation "substance" is withdrawn in response to Applicants' amendment of the claim deleting "substance."

Claim Rejections - 35 USC § 112, first paragraph—Written Description

The rejection of claims 12, 16-28 and 30-43 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicants' arguments and evidence presented at pages 9 and 10 and in response to Applicants' cancellation of claim 30.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph—Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 12, 16-28 and 31-43 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Upon reconsideration, the specification, while being enabling for the claimed methods of administering FSH or an FSH variant, wherein said variant has agonist activity, does not reasonably provide enablement for the FSH variants as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicants argue at pages 7 and 8 that some experimentation and/or screening does not make a claim non-enabled so long as the experimentation is routine, and that it would take only routine experimentation for the skilled artisan to distinguish variants with FSH antagonist activity, since FSH was well known in the art and its structure-function relationship has been well studied, using articles cited by the Examiner to support their position.

This argument has been fully considered but is not found persuasive. As noted in the previous Office action mailed 29 October 2009, some FSH variants are antagonistic in their activity. The Examiner pointed out that since experiments have shown that FSH blockade resulted in declining male fertility and impairment of testicular function, an FSH variant with antagonist properties, which is encompassed by the claims, would not be expected to successfully treat male infertility. In response, Applicants point out that the skilled artisan could distinguish variants with FSH antagonist activity. However, the claimed methods are methods of treating male infertility, not merely screening methods for FSH variants with agonist vs. antagonist activity. The nature of the invention, namely, the reduction and treatment of gamete chromosomal abnormalities and treatment of male infertility is complex. Currently in

vitro fertilization (IVF) procedures represent the best available treatment of male infertility. Nevertheless, success rates for IVF remain quite low; for instance, see Acosta et al. (of record) who report at p. 1150, left column that many oligozoospermic males do not experience positive IVF outcomes. Thus the art provides evidence of the difficulty in treating of male infertility. Since IVF is a difficult and expensive undertaking, it would not be routine to make and test all the FSH variants encompassed by the claims. Regardless of the level of difficulty in screening for FSH variants with agonist vs. antagonist activity, carrying out the empirical experimentation in order to establish efficacy of the encompassed FSH variants would not be routine.

Due to the large quantity of experimentation necessary to determine if FSH variants with antagonistic activity would be useful in treating or reducing gamete numerical chromosomal alterations in males, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention, the state of the art which teaches many FSH variants that antagonize FSH activity, (the level of skill of those in the art), the unpredictability regarding whether such antagonists could be used to treat or reduce gamete numerical chromosomal alterations in males, and the breadth of the claims which fail to recite limitations on FSH variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 12, 16, 17, 19-27, 31-33, 35-39 and 41-43 under 35 U.S.C. 102(b) as being anticipated by Acosta et al. (Fertil Steril. 1991; 55: 1150-6—of record) as evidenced by Moeman et al. (Andrologia, 2008; 40: 381-386) as set forth in the Office action mailed 29 October 2009 is maintained for reasons of record and the following.

Applicants argue at pages 10 and 11 that in order to establish inherency, the Office cannot merely demonstrate that the asserted limitation is probable or possible, and that Moeman et al. fail to make clear that the missing descriptive matter is necessarily present since that the mean percentages of XX an XY disomy are 0.18% and 0.37% in OAT males (0.1% and 0.17%, respectively in healthy controls) and that the mean percentage of YY disomy was non-significant, further arguing that "mean percentage or mean frequency does not make clear whether any of the individual patients in Acosta et al. would necessarily have gamete chromosomal alterations."

This argument has been fully considered but is not found persuasive. This synopsis of the data in Moeman et al. leaves out very important information, namely a minimum of 1500 sperm nuclei per individual for each chromosome were evaluated in severe OAT and a minimum of 5000 sperm nuclei per individual in normozoospermic men were evaluated, thus 165,000 sperm were evaluated in total. Further, the results for XX and XY disomy frequencies were ***statistically significant***. The P values were 0.001, which means there is only a 0.001% likelihood that the findings of higher incidences of XX and XY disomy in sperm nuclei from OAT males is due to random occurrence. One of ordinary skill in the art would understand that these data make

clear that individual patients in Acosta et al. would necessarily have a higher incidence of gamete chromosomal alterations. Finally, with respect to Applicants' argument regarding the non-significance of the incidence of YY disomy between OAT patients and normozoospermic males, the claims are drawn only to "gamete chromosomal numerical alterations."

Applicants argue at p. 11 that the claims require diagnosing a male as having XX disomy or YY disomy and administration of FSH for reducing or treating the rate of gamete numerical chromosomal alterations in a male and assert that Acosta does not appear to teach diagnosing a male with XX or YY disomy or diagnosing a male with gamete chromosomal alterations. (It is not clear what Applicants are arguing in the preceding line: "The Acosta reference does not indicate that administration of FSH to male patients nor does…"

This argument has been fully considered but is not found persuasive. The Acosta reference clearly discusses diagnosis using the same criteria as are outlined in the specification at pages 6 and 7 (see p. 1151 of Acosta et al., under Materials and Methods). Acosta et al. disclose patients having the same level of extreme male infertility characterized by low sperm concentration, impaired motility and abnormal morphology that was taught in Moeman et al. (See p. 1151, 3rd paragraph of Acosta et al.). The Moeman reference provides evidence that there is a significant correlation between OAT and XX and XY disomy, thus they teach that semen quality do equate with XX and XY gamete chromosomal alteration in individuals.

Applicants argue at p. 12 that Moeman et al. indicate that semen quality does not universally equate gamete chromosomal alteration in individuals since it cannot provide information on the condition of the male genome contained in sperm heads.

This argument has been fully considered but is not found persuasive. Applicants have taken this quote out of context. The very purpose of the work of Moeman and

colleagues was aimed "to determine the incidence of sperm disomy in infertile men with idiopathic severe OAT," (see the abstract) since traditional semen quality parameters do not provide genetic information. There is no such strong statement that "that semen quality does not equate gamete chromosomal alteration in individuals," as suggested by Applicants. What Moeman et al. actually found was that there was a significant correlation between OAT and XX and XY disomy, thus their findings suggest that semen quality parameters do indeed equate with XX and XY gamete chromosomal alteration in individuals. Acosta et al. diagnose patients as infertile using sperm quality parameters including low sperm concentration, impaired motility and abnormal morphology that encompasses a population of males with OAT and Moeman et al. provide evidence that infertile OAT patients have an increased frequency of XX and XY disomy in their spermatozoa. Thus, it is evident that Acosta et al. are administering the same compound (FSH) to the same patient population as required by the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 18 and 34 under 35 U.S.C. 103(a) as being unpatentable over Acosta et al. (cited above—of record) and as applied to claims 12, 16, 17, 19-27, 31-33, 35-39 and 41-43 above and further in view of Loumaye et al. (Hum Reprod Update. 1995; 1: 188-99) as set forth in the Office action mailed 29 October 2009 is maintained for reasons of record and the following.

Applicants argue at p. 12 that Loumaye et al. do not cure the defect of Acosta et al. and fails to teach the diagnosis of gamete chromosomal abnormalities in males.

This argument has been fully considered but is not found persuasive. Loumaye et al. does not need to cure any defects in Acosta et al., since the Examiner does not find Acosta et al. deficient for the reasons outlined above in the rejection under 35 U.S.C. § 102(b), which are hereby incorporated. Further, the only new limitation in claims 18 and 34 is the administration of recombinant or rFSH, which is a variant of FSH, and Loumaye et al. teach how rFSH is made and that rFSH is safe and effective because it had greater purity than urinary FSH.

As discussed in the previous Office Action, it would be obvious to one of ordinary skill in the prior art (POSITA) to substitute rFSH for FSH because the level of skill in the art concerning knowledge of recombinant methods for making recombinant gonadotropins is high, and given the evidence presented in Loumaye et al. that the rFSH was well tolerated, the POSITA could expect to substitute rFSH for pure FSH with a reasonable expectation of success. The final issue is to consider objective evidence

present in the application indicating obviousness or nonobviousness. Nowhere in the application is a surprising or unexpected result taught with respect to administration of rFSH over and above what is taught in the prior art.

The rejection of claims 28 and 40 under 35 U.S.C. 103(a) as being unpatentable over Acosta et al. (cited above—of record) and as applied to claims 31-33, 35-39 and 41-43 above and further in view of Bouloux et al. (Human Reprod. 2001, 16: 1592-1597—of record) is maintained for reasons of record and the following.

Applicants argue at p. 13 that Bouloux et al. do not cure the defect of Acosta et al.

This argument has been fully considered but is not found persuasive. Bouloux et al. does not need to cure any defects in Acosta et al., since the Examiner does not find Acosta et al. deficient for the reasons outlined above in the rejection under 35 U.S.C. § 102(b), which are hereby incorporated. Further, the only new limitation in claims 18 and 40 is the administration of CTP-FSH, which is a variant of FSH. Bouloux et al. teach that CTP-FSH is safe and effective because it could lead to more convenient dosing regimens. Given this teaching, it would be obvious to the POSITA to substitute CTP-FSH for FSH because the level of skill in the art concerning knowledge of how to make and use CTP-FSH is high, and given the evidence presented in Bouloux et al. that the FSH-CTP was well tolerated, the POSITA could expect to substitute FSH-CTP for pure FSH with a reasonable expectation of success. The final issue is to consider objective evidence present in the application indicating obviousness or nonobviousness. Nowhere

in the application is a surprising or unexpected result taught with respect to administration of FSH-CTP over and above what is taught in the prior art.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Ushijima et al. (Human Reprod. 2000; 15: 1107-1111) teach that there is significantly higher frequency of sex chromosome (i.e. XX and YY) disomy in OAT males (see abstract; whole document; also Figure 1, p. 1109).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest

/Bridget E Bunner/
Primary Examiner, Art Unit 1647